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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/725,030	11/29/2000	Ashley Stuart Davis		8960

7590 06/24/2003

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,030	DAVIS ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 3-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 3-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 16 (filed 2/25/03), claims 3-7 have been amended. Claims 3-7 remain pending.

Applicants' arguments filed 2/25/03 have been considered and found persuasive in part.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have provided data which shows that representative compounds are (a) effective to inhibit microtubule polymerization, and (b) effective to inhibit growth of cancer cells. Based on this, applicants are asserting that the claimed compounds will be therapeutically effective to treat a human who is afflicted with a fungal infection, a viral infection or a parasitic infection. It is also asserted that the claimed compounds will be therapeutically effective to treat a human who is afflicted with gout, restenosis, MS, Parkinson's or Alzheimer's Disease. However, no reason is given in the specification as to why a

skilled cell biologist would believe that if a compound is effective to inhibit microtubule polymerization *in vitro*, or growth of cancer cells *in vitro*, the compound will be effective to treat any of the cited disorders. The specification provides no parallels from the prior art which would suggest that there is any basis for the proposed extrapolation. It is noted that there are assertions in the literature that colchicine can be used to treat gout, but (a) it does not appear that there is any mention of this in the specification, and (b) it is not the case that all compounds which are effective to inhibit microtubule polymerization will be effective to treat gout.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Taking the treatment of fungal infections as an example, applicants have not shown that growth or proliferation of a fungus can be inhibited, even *in vitro*. But if, at some point in the future, applicants were to provide data which showed that growth or proliferation of a fungus can be inhibited *in vitro*, the question would then become, can a skilled cell biologist or mycologist "predict" therapeutic efficacy on the basis of such *in vitro* data? As it happens, one cannot reliably

predict therapeutic efficacy merely because a compound can inhibit proliferation of a fungus in vitro. Consider the following:

- Buchta, V. (*Mycoses* **44** (11-12) 505-12, 2001) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.

- Adam (*Medicine* **65**, 203, 1986) discloses (page 208, col 2) that *in vitro* susceptibility to antifungal agents did not correlate with therapeutic efficacy of the agents.

- Nagasawa M. (*Journal of Infection* **44** (3) 198-201, 2002) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.

- Manfredi R (*Mycopathologia* **148** (2) 73-8, 1999) discloses that two patients died from a cyrotpococcus infection despite being treated with an agent that exhibited anti-fungal activity *in vitro*.

- Wang M. X. (*Cornea* **19** (4) 558-60, 2000) discloses that a patient was treated with an agent that exhibited anti-fungal activity *in vitro*, but that despite this, his fungal sclerokeratitis progressed to endophthalmitis.

- Bhalodia M V (*Journal of the Association for Academic Minority Physicians* **9** (4) 69-71, 1998) discloses that a compound that exhibited anti-fungal activity *in vitro* was not effective to treat a candida infection in a patient.

- Moore M. L. (*Journal of Perinatology* **21** (6) 399-401, 2001) discloses that a premature infant died from a fungal infection despite being treated with a compound that exhibits anti-fungal activity *in vitro*.

- Berman, Judith (*Nat Rev Genet* **3** (12) 918-30, 2002) discloses that many immunocompromised patients die from *Candida* infections in spite of having received various dosages of compounds which exhibit anti-fungal activity *in vitro*.

- van Duin David (*Antimicrobial Agents and Chemotherapy* **46** (11) 3394-400, 2002) has disclosed an example of a compound which exhibits antifungal activity *in vitro* but not *in vivo*.

- Marr K. A. (*Antimicrobial Agents and Chemotherapy* 45 (1) 52-9, 2001) discloses that a patient developed a fungal infection despite prophylactic treatment with a compound which exhibits antifungal activity *in vitro*.

In accordance with the foregoing, one cannot "predict" therapeutic efficacy on the basis of fungal growth inhibition *in vitro*. In addition, applicants have not even taken the first step in the process of providing evidence, which would be to show that the claimed compounds can inhibit proliferation of fungi *in vitro*.

Consider next the matter of treating parasitic infections. Again, there is no evidence that proliferation of parasites can be reduced or inhibited *in vitro* or *in vivo*. The following references discuss the matter of parasitic infections in animals and humans:

Urbani C (*Tropical Medicine and International Health* 6 (11) 935-44, 2001)

Geerts S (*Clinical Microbiology Reviews* 13 (2) 207-22, 2000)

Larsen, M (*International Journal for Parasitology* 29 (1) 139-46, 1999)

Stephenson (*Drugs* 60 (5) 985-95, 2000);

Cutrona (*Comprehensive Therapy*, 20 (8) 445-58, 1994)

Mandell (*Medical Clinics of North America* 72 (3) 669-90, 1988).

Roos M. H. (*Pharmacology and Therapeutics* **60** (2) 331-6, 1993

Borst P. (*Annual Review of Microbiology* **49**, 427-60, 1995)

Tarleton (*International Journal for Parasitology* **31**(5-6) 550-554, 2001)

Docampo (*Current Pharmaceutical Design* 7(12) 1157-64, 2001)

Parasitic infections include malaria, trypanosomiasis, schistosomiasis, onchocerciasis, leishmaniasis, amebiasis, ascariasis, babesiosis, balantidiasis, enterobius, fiarisis, blood flukes, giaridasis, hookworm, strongyloidiasis, tapeworm, toxoplasmosis, trichinosis, and trichuriasis. As it happens, the specification does not teach a skilled medical practioner to treat any of these diseases in humans or animals. As the references explain, treatment of parasitic infections in humans and animals is often unsuccessful. For example, as conveyed in the references, many parasites develop resistance to chemical agents. Treatment of Chagas disease, for example, is particularly difficult. How do applicants propose to treat this disease using the claimed compounds? Thus, even if applicants had shown that the compounds are effective to inhibit proliferation of parasites *in vitro*, "undue experimentation" would be required to make the transition to treatment of parasitic infections in humans.

As for restenosis, M.S., Parkinson's and Alzheimer's Disease, no rationale has been provided as to why a compound which is effective to inhibit microtubule polymerization or to inhibit growth of cancer cells would be effective to treat any of these disorders. Furthermore, no such rationale is apparent. Accordingly, "undue experimentation" would be required to practice the invention of claim 7.

In the amendment filed 2/27/03, applicants have stated that claim 7 should be deleted.

However, applicants have provided no directive to delete this claim. Accordingly, claim 7 is still regarded as pending. It is suggested that applicants supply a clear directive to cancel claim 7.

*

Claims 3-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,294,695. Although the conflicting claims are not identical, they are not patentably distinct from each other.

In response to this ground of rejection, applicants have argued that while the compounds of figure 1a and 1b are disclosed in USP '695, the mechanism of action that is disclosed in USP '695 (for these compounds) is not the same as that asserted in the instant application. However, novelty of a specific compound does not accrue merely by asserting a different use of that compound, or a different effect of the compound. The compounds of figure 1a and 1b were disclosed and claimed in USP '695. **All properties** of the '695 compounds, without exception, are completely indistinguishable from the compounds of figure 1a and 1b (of the instant application). The G1/S phase cell cycle arrest effect is inherent in the '695 compounds. Furthermore, the law is very clear on this point. (See, e.g., *Ex parte Novitski* (26 USPQ2d 1389, 1993); *Bristol-Myers Squibb v. Ben Venue Laboratories* (58 USPQ2d 1508, 2001); *In re May and Eddy* (197 USPQ 601)).

Consider this matter from another perspective. Consider hypothetical claims 100-102

below:

100. The compound aspirin.

101. A compound according to claim 100 which is effective to inhibit prostaglandin biosynthesis.

102. A compound according to claim 100 which is effective to inhibit nuclear factor kappa B.

103. A compound according to claim 100 which is effective to stimulate production of growth hormone.

104. A compound according to claim 100 which is effective to antagonize the progesterone receptor.

Certainly, applicants would recognize that in the year 2003, a claim to aspirin would not be novel. Perhaps also, applicants would recognize that claims 101 and 102 are not novel either, since these properties of aspirin are known. But suppose that an applicant were to assert that aspirin could stimulate production of growth hormone, or that it could antagonize the progesterone receptor. As it happens, claims 103 and 104 could be properly rejected over any reference which discloses aspirin, even if the reference made no mention of growth hormone or the progesterone receptor. If indeed aspirin does exhibit these effects, such properties will necessarily be inherent in the compound, regardless of who is in possession of the compound.

The rejection is valid, and is maintained. It is suggested that a terminal disclaimer be filed.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d)

*

Claims 3-7 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 3 is viewed as consisting of two sentences. A claim should consist of one sentence only. (Applicants should be aware that the record should be clear to various persons in addition to the examiner. This is especially true of the claims, which must be entirely clear to various PTO personnel, as well as being clear to the persons who are responsible for printing the final document).

- Claims 4-6 make reference to a figure 1a. However, the claims should stand on their own, without reference to other locations in the application. It is suggested that the structure of figure 1a be introduced into each of claims 4-6.

- Claim 6 is indefinite as to the intended derivative.

- Claim 7 recites "may have therapeutic potential". This language renders the claim indefinite as to whether the tubulin ligand is therapeutically effective or not.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3 and 5-7 are rejected under 35 U.S.C. §102(a) as being anticipated by Jiang (*Cancer Research* **58**, 2126, 1998).

Jiang discloses (table 1, page 2127) the compound designated "3-BAABE". This compound falls within the scope of the genus of compounds depicted in figure 1a of the instant application. Jiang discloses that this compound induces apoptosis.

As indicated, the reference discloses that the compound "3-BAABE" induces apoptosis. The properties of this compound that are asserted in the instant specification are inherent in the prior art compound. In fact, the properties of the compound that are asserted in the reference are largely irrelevant to the question of anticipation. All that matters is that the structure of the compound is identical to one of those claimed. If the reference had disclosed that the compound "3-BAABE" had no use other than as an additive for an industrial cleaning fluid, the rejection would be equally valid. If such had been the disclosure of the reference, the property of inhibiting the G1/S transition would still be inherent.

The claims are anticipated.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness

rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 3 and 7 are rejected under 35 U.S.C. §103 as being unpatentable over Jiang (*Anti-cancer Drug Design* **13**, 735, 1998) in view of Alberts (*The Molecular Biology of the Cell*, 2nd Ed., 1989, pages 727 - 786).

Jiang discloses that compounds 6-9 (page 736) induce mitotic arrest. Jiang does not disclose that, as a consequence of inducing mitotic arrest, the transition of a cell from the "G1" phase to the "S" phase will also be inhibited. Alberts discusses the processes involved in cell division and discloses (e.g., page 728 and 729) that the cell cycle may be represented as follows:

$$G1 \rightarrow S \rightarrow G2 \rightarrow M \rightarrow G1 \rightarrow \text{etc.}$$

That is, beginning with e.g., G1, the next phase is "S"; this is followed by G2, which is followed by "M", which is followed once again by G1. The point is that this is a cycle.

If any one "phase" or section of the cycle is inhibited, then all other phases of the cycle must be inhibited as well. If, for example, a given agent inhibits the G2→M transition, or the M→G1 transition of a given population of cells, the number of cells which will undergo the G1 → S transition will be decreased. If, in a single cell, the G2→M transition or the M→G1 transition is blocked entirely, then that cell will stop undergoing the G1/S transition.

Consider what is <u>not</u> being claimed. The following is not being claimed:

> *A tubulin ligand that causes a G1/S phase cell cycle arrest mechanism, with the proviso that the rate of transition through the G2/M phase is completely unaffected by the tubulin ligand, and with the further proviso that mitosis is not inhibited.*

There is no exclusion of G2/M phase inhibition, no exclusion of mitosis inhibition, and no exclusion of necrosis inhibition. Given the absence of any such exclusion, all of these processes are included.

Thus, a cell biologist of ordinary skill would recognize that by inducing mitotic arrest, the G1/S transition will be inhibited, along with all other phases of the cell cycle.

*

Claims 3 and 7 are rejected under 35 U.S.C. §103 as being unpatentable over Abraham I. (*Proc Natl. Acad. Sci.* 83, 6839-43, 1986) in view of Alberts (*The Molecular Biology of the Cell*, 2nd Ed., 1989, pages 727 - 786).

Abraham discloses that DCBT inhibits mitosis and inhibits polymerization of microtubules.

Abraham does not disclose that, as a consequence of inhibiting mitosis, the transition of a cell from the "G1" phase to the "S" phase will also be inhibited. Alberts discusses the processes involved in cell division and discloses (e.g., page 728 and 729) that the cell cycle may be represented as follows:

$$G1 \rightarrow S \rightarrow G2 \rightarrow M \rightarrow G1 \rightarrow \text{etc.}$$

There is no exclusion of G2/M phase inhibition, and no exclusion of mitosis inhibition. Accordingly, compounds which inhibit both of these processes, in addition to G1/S, are included.

Thus, a cell biologist of ordinary skill would recognize that by inducing mitotic arrest, the G1/S transition will be inhibited, along with all other phases of the cell cycle.

*

Claims 3 and 7 are rejected under 35 U.S.C. §103 as being unpatentable over Sorger P.K. (*Curr Opin Cell Biol.* **9**, 807-814, 1997) in view of Alberts (*The Molecular Biology of the Cell*, 2nd Ed., 1989, pages 727 - 786).

Sorger discloses various compounds that inhibit microtubule polymerization, resulting in cell cycle delay or apoptosis. Sorger does not disclose that, as a consequence of inducing apoptosis or delaying the cell cycle, the transition of a cell from the "G1" phase to the "S" phase will be inhibited, or eliminated altogether. Alberts discusses the processes

involved in cell division and discloses (e.g., page 728 and 729) that the cell cycle may be represented as follows:

$$G1 \rightarrow S \rightarrow G2 \rightarrow M \rightarrow G1 \rightarrow \text{etc.}$$

Thus, a cell biologist of ordinary skill would recognize that by delaying the cell cycle, or causing cell death, the G1/S transition will be inhibited or eliminated altogether.

Thus, the claims are rendered obvious.

*

Claims 3 and 7 are rejected under 35 U.S.C. §103 as being unpatentable over Jordan (*Current Opinion in Cell Biology* **10** (1) 123-30, 1998) in view of Alberts (*The Molecular Biology of the Cell*, 2nd Ed., 1989, pages 727 - 786).

Jordan discloses various agents which inhibit mitosis. Jordan does not disclose that, as a consequence of inhibiting mitosis, the transition of a cell from the "G1" phase to the "S" phase will also be inhibited. Alberts discusses the processes involved in cell division and discloses (e.g., page 728 and 729) that the cell cycle may be represented as follows:

$$G1 \rightarrow S \rightarrow G2 \rightarrow M \rightarrow G1 \rightarrow \text{etc.}$$

Thus, a cell biologist of ordinary skill would recognize that by inducing mitotic arrest, the G1/S transition will be inhibited, along with all other phases of the cell cycle.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800